CLAIMS

What is claimed is:

1. A method of inhibiting stenosis or restenosis of a blood vessel following vascular injury in a subject, comprising administering to said subject a therapeutically effective amount of a first therapeutic agent and a therapeutically effective amount of a second therapeutic agent, wherein

said first therapeutic agent inhibits the adhesion and/or recruitment of neutrophils to a site of vascular injury; and

said second therapeutic agent inhibits the adhesion and/or recruitment of mononuclear cells to a site of vascular injury.

2. The method of Claim 1, wherein said vascular injury arises from a vascular intervention procedure.

3. The method of Claim 2, wherein said procedure is selected from the group consisting of angioplasty, vascular by-pass surgery, vascular grafting, endarterectomy, atherectomy, endovascular stenting, insertion of prosthetic valve and transplantation of organs, tissues or cells.

4. The method of Claim 1, wherein said first therapeutic agent is a cellular adhesion molecule antagonist.

5. The method of Claim 4, wherein said first therapeutic agent is an integrin antagonist.

6. The method of Claim 5, wherein said antagonist inhibits cellular adhesion mediated through a β2 integrin.

7. The method of Claim 6, wherein said β2 integrin is selected from the group consisting of CD11a/CD18, CD11b/CD18, CD11c/CD18 and CD11d/CD18.

8. The method of Claim 4, wherein said cellular adhesion molecule antagonist is an antibody or antigen-binding fragment thereof.

9. The method of Claim 8, wherein said antibody or antigen-binding fragment binds an integrin.

10. The method of Claim 9, wherein said antibody or antigen-binding fragment binds CD18.

11. The method of Claim 1, wherein said second therapeutic agent is a cell adhesion molecule antagonist.

12. The method of Claim 1, wherein said second therapeutic agent is an antagonist of chemokine receptor function.

13. The method of Claim 12, wherein said chemokine receptor is a CC chemokine receptor.

14. The method of Claim 12, wherein said antagonist of chemokine receptor function is an antibody or antigen-binding fragment thereof.

15. The method of Claim 14, wherein said antibody or antigen-binding fragment binds a CC-chemokine receptor.

16. The method of Claim 15, wherein said antibody or antigen-binding fragment binds CC-chemokine receptor 2.

17. The method of Claim 12, wherein said antagonist of chemokine receptor function is a small organic molecule.

18. A method of inhibiting stenosis or restenosis of a blood vessel following angioplasty in a subject, comprising administering to said subject a therapeutically effective amount of a first therapeutic agent and a therapeutically effective amount of a second therapeutic agent, wherein

said first therapeutic agent is an antibody or antigen-binding fragment thereof which binds a cellular adhesion molecule and thereby inhibits the adhesion and/or recruitment of neutrophils to a site of vascular injury; and

said second therapeutic agent is an antagonist of CCR2 function.

19. The method of Claim 18, wherein said angioplasty is percutaneous transluminal coronary angioplasty.

20. The method of Claim 18, wherein said angioplasty includes placement of a stent.

21. The method of Claim 18, wherein said first therapeutic agent binds a β2 integrin.

22. The method of Claim 18, wherein said first therapeutic agent binds CD18.

23. The method of Claim 18, wherein said second therapeutic agent is an antibody or antigen-binding fragment thereof.

24. A method of inhibiting stenosis or restenosis of a blood vessel following a vascular intervention procedure which includes the placement of a stent in a subject, comprising administering to said subject a therapeutically effective amount of a first therapeutic agent and a therapeutically effective amount of a second therapeutic agent, wherein

said first therapeutic agent is an antibody or antigen-binding fragment thereof which binds a cellular adhesion molecule and thereby inhibits the adhesion and/or recruitment of neutrophils to a site of vascular injury; and

said second therapeutic agent is an antagonist of CCR2 function.

25. The method of Claim 24, wherein said vascular intervention procedure is angioplasty.

26. The method of Claim 24, wherein said first therapeutic agent is an antibody or antigen-binding fragment thereof which binds a β2 integrin.

27. The method of Claim 24, wherein said first therapeutic agent binds CD18.

28. The method of Claim 27, wherein said second therapeutic agent is an antibody or antigen-binding fragment thereof which binds CCR2.

29. A method of inhibiting stenosis or restenosis of a blood vessel following vascular injury in a subject, comprising administering to said subject a therapeutically effective amount of an agent which inhibits the adhesion and/or recruitment of neutrophils and mononuclear cells to a site of vascular injury.

30. A method of inhibiting stenosis or restenosis of a blood vessel following a vascular intervention procedure which includes the placement of a stent in a subject, comprising administering to said subject a therapeutically effective amount of a first therapeutic agent and a therapeutically effective amount of a second therapeutic agent, wherein

said first therapeutic agent is an anti-CD18 antibody or antigen-binding fragment thereof which binds CD18 and inhibits binding of a ligand to an integrin which contains CD18, wherein said anti-CD18 antibody or antigen-binding fragment comprises light chain complementarity determining regions (CDR1, CDR2 and CDR3) of nonhuman origin, heavy chain complementarity determining regions (CDR1, CDR2 and CDR3) of nonhuman origin, and at least a portion of an immunoglobulin of human origin, wherein said light chain complementarity determining regions and said heavy chain complementarity determining regions have the amino acid sequences set forth below:

light chain: CDR1 the amino acid sequence of SEQ ID NO:2
CDR2 the amino acid sequence of SEQ ID NO:3
CDR3 the amino acid sequence of SEQ ID NO:4

heavy chain: CDR1 the amino acid sequence of SEQ ID NO:6
CDR2 the amino acid sequence of SEQ ID NO:7
CDR3 the amino acid sequence of SEQ ID NO:8;

said second therapeutic agent is an anti-CCR2 antibody or antigen-binding fragment thereof which binds CCR2 and inhibits binding of a ligand to said CCR2, wherein said anti-CCR2 antibody or antigen-binding fragment comprises light chain complementarity determining regions (CDR1, CDR2 and CDR3) of nonhuman origin, heavy chain complementarity determining regions (CDR1, CDR2 and CDR3) of nonhuman origin, and at least a portion of an immunoglobulin of human origin, wherein said light chain complementarity

determining regions and said heavy chain complementarity determining regions have the amino acid sequences set forth below:

light chain: CDR1 the sequence of amino acids 24-39 of SEQ ID NO:11
CDR2 the sequence of amino acids 55-61 of SEQ ID NO:11
CDR3 the sequence of amino acids 94-102 of SEQ ID NO:11

heavy chain: CDR1 the sequence of amino acids 31-35 of SEQ ID NO:12
CDR2 the sequence of amino acids 50-68 of SEQ ID NO:12
CDR3 the sequence of amino acids 101-106 of SEQ ID NO:12.

31. The method of Claim 30, wherein said anti-CD18 antibody or antigen-binding fragment comprises a light chain variable region having the amino acid sequence of SEQ ID NO:10 and heavy chain variable region having the amino acid sequence of SEQ ID NO: 9.

32. The method of Claim 30, wherein said anti-CCR2 antibody or antigen-binding fragment comprises:

a light chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 and SEQ ID NO: 18; and

a heavy chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23.

33. The method of Claim 32, wherein said light chain variable region has the amino acid sequence of SEQ ID NO: 14, and said heavy chain variable region has the amino acid sequence of SEQ ID NO: 20.

34. A method of inhibiting stenosis or restenosis of a blood vessel following a vascular injury, comprising administering to said subject a therapeutically effective amount of a first therapeutic agent and a therapeutically effective amount of a second therapeutic agent, wherein

said first therapeutic agent is an anti-CD18 antibody or antigen-binding fragment thereof which binds CD18 and inhibits binding of a ligand to an integrin which contains CD18, and

said second therapeutic agent is an anti-CCR2 antibody or antigen-binding fragment thereof which binds CCR2 and inhibits binding of a ligand to said CCR2.

35. The method of Claim 34, wherein said anti-CD18 antibody or antigen-binding fragment thereof inhibits binding of a ligand selected from the group consisting of ICAM-1, ICAM-2 and fibrinogen to an integrin selected from the group consisting of CD11a/CD18, CD11b/CD18, CD11c/CD18 and CD11d/CD18.

36. The method of Claim 34, wherein said anti-CCR2 antibody or antigen-binding fragment thereof inhibits binding of a ligand selected from the group consisting of MCP-1, MCP-2, MCP-3, MCP-4 and MCP-5 to said CCR2.

37. The method of Claim 34, wherein said vascular injury arises from a vascular intervention procedure.

38. The method of Claim 37, wherein said vascular intervention procedure is selected from the group consisting of angioplasty, vascular by-pass surgery, vascular grafting, endarterectomy, atherectomy, endovascular stenting, insertion of prosthetic valve and transplantation of organs, tissues or cells.

39. The method of Claim 37, wherein said vascular intervention procedure comprises placement of a stent.